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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Triclopyr Qualitative Risk Assessment Based On Fischer-344 Rat and Jcl:ICR Mouse Dietary Studies

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Summary

This qualitative risk assessment of Triclopyr was based upon chronic dietary studies conducted in Fischer-344 rats and Jcl:ICR mice. The rats received 0, 3, 12, or 36 mg/kg/day of Triclopyr for 105 weeks. The mice received 0, 50, 250, or 1250 ppm of Triclopyr for 95 weeks.

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Triclopyr in male or female rats.

Although male rats had no significant dose-related increasing trends, there were significant differences in the pair-wise comparisons of the 3 and 12 mg/kg/day dose groups with the controls for adrenal gland benign pheochromocytomas and benign and/or malignant pheochromocytomas combined, and skin fibromas. There was also a significant difference in the pair-wise comparison of the 12 mg/kg/day dose group with the controls for skin papillomas. These significant differences should be interpreted cautiously as only those animals with macroscopic observations in the 3 and 12 mg/kg/day dose groups had microscopic skin examinations.

Female rats had significant dose-related increasing trends in mammary gland adenocarcinomas and adenomas and/or adenocarcinomas combined, and a significant difference in the pair-wise comparison of the 36 mg/kg/day dose group with the controls for mammary gland adenomas and/or adenocarcinomas combined. All animals in the 3 and 12 mg/kg/day dose groups were not examined microscopically for mammary gland tumors.

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Triclopyr in male or female mice.

There were no compound-related tumors observed in male mice.

Female mice had a significant dose-related increasing trend in mammary gland adenocarcinomas, although there were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

Background

A chronic toxicity and carcinogenicity study in Fischer-344 rats was conducted by the Mammalian and Environmental Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, for DowElanco, Indianapolis, Indiana, and issued January 27, 1987 (Study No. K-042085-026; MRID No. 401077-01).

The study design allocated groups of 50 rats per sex to dose levels of 0, 3, 12, or 36 mg/kg/day of Triclopyr for 105 weeks. An additional 20 rats per sex per dose were designated for interim sacrifice, 10 each at weeks 27 and 54.

A chronic toxicity and carcinogenicity study in Jcl:ICR mice was conducted by the Institute of Environmental Toxicology, Tokyo, Japan, for Dow Chemical Japan, Ltd., Tokyo, Japan, and issued April, 1987 (MRID No. 403566-01).

The study design allocated groups of 80 mice per sex to dose levels of 0, 50, 250, or 1250 ppm of Triclopyr for 95 weeks. An additional 20 mice per sex per dose were designated for interim sacrifice, 10 each at weeks 26 and 52.

Survival Analyses

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Triclopyr in male or female rats or mice. See Tables 1 and 2 for rat

mortality test results, and Tables 7 and 8 for mouse mortality test results.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analyses

Male rats had no significant increasing trends, although there were significant differences in the pair-wise comparisons of the 3 mg/kg/day dose group with the controls for adrenal gland benign pheochromocytomas and benign and/or malignant pheochromocytomas combined, and skin fibromas, all at $p < 0.05$. There were also significant differences in the pair-wise comparisons of the 12 mg/kg/day dose group with the controls at $p < 0.01$ for both adrenal gland benign pheochromocytomas and benign and/or malignant pheochromocytomas combined, and at $p < 0.05$ for both skin fibromas and skin papillomas. The significant pair-wise comparisons of the 3 and 12 mg/kg/day dose groups with the controls for skin fibromas and papillomas should be interpreted carefully, as only those animals with macroscopic observations in these dose groups had microscopic skin examinations.

Female rats had significant increasing trends in mammary gland adenocarcinomas at $p < 0.05$ and in adenomas and/or adenocarcinomas combined at $p < 0.01$. There was a significant difference in the pair-wise comparison of the 36 mg/kg/day dose group with the controls for mammary gland adenomas and/or adenocarcinomas combined at $p < 0.05$. Only those animals with macroscopic observations in the 3 and 12 mg/kg/day dose groups were examined microscopically for mammary gland tumors.

There were no compound-related tumors observed in male mice.

Female mice had a significant increasing trend in mammary gland adenocarcinomas at $p < 0.05$. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

The statistical analyses of the male and female rats and the female mice were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Tables 3 through 6 for rat tumor analysis results. See Table 9 for mouse tumor analysis results.

Table 1. Triclopyr - Fischer-344 Rat Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Weeks 1-26	27[i]	27-53	54[i]	54-78	79-106[f]	Total
0	0/70	10/70	0/60	10/60	2/50	23/48	25/50 (50)
3	0/70	10/70	1/60	10/59	2/49	13/47	16/50 (32)
12	0/70	10/70	0/60	10/60	1/50	12/49	13/50 (26)**[n]
36	0/70	10/70	0/60	10/60	1/50	17/49	18/50 (36)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifices at weeks 27 and 54.

[f]Final sacrifice at week 105.

[n]Negative change from control.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Triclopyr - Fischer-344 Rat Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Weeks 1-26	27[i]	27-53	54[i]	54-78	79-106[f]	Total
0	0/70	10/70	1/60	10/59	1/49	8/48	10/50 (20)
3	0/70	10/70	0/60	10/60	0/50	7/50	7/50 (14)
12	0/70	10/70	0/60	10/60	1/50	8/49	9/50 (18)
36	0/70	10/70	0/60	10/60	1/50	8/49	9/50 (18)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifices at weeks 27 and 54.

[f]Final sacrifice at week 106.

[n]Negative change from control.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 3. Triclopyr - Fischer-344 Rat Study

Male Adrenal Gland Pheochromocytoma Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	3	12	36
Benign (%)	6/50 (12)	14[a]/49 (29)	17/50 (34)	12/50 (24)
p =	0.282	0.035*	0.008**	0.096
Malignant (%)	0/50 (0)	2[b]/49 (4)	3/50 (6)	0/50 (0)
p =	0.275	0.242	0.121	1.000
Combined (%)	6/50 (12)	16/49 (33)	20/50 (40)	12/50 (24)
p =	0.376	0.012*	0.001**	0.096

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

[a]First benign pheochromocytoma observed at week 85, 3 mg/kg/day.

[b]First malignant pheochromocytoma observed at week 95, 3 mg/kg/day.

Note: No animals in either of the interim sacrifice groups had any adrenal gland pheochromocytomas. Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. Triclopyr - Fischer-344 Rat Study

Male Skin Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	3	12	36
Fibromas (%)	1[a]/50 (2)	4/23[#] (17)	5/23[#] (22)	5/50 (10)
p =	0.297	0.032*	0.011*	0.102
Papillomas (%)	0/50 (0)	0/23[#] (0)	3/23[#] (13)	3[b]/50 (6)
p =	0.108	1.000	0.029*	0.121

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

[a]First fibroma observed at week 93, dose 0 mg/kg/day.

[b]First papilloma observed at week 97, dose 36 mg/kg/day.

[#]Only those animals in the 3 and 12 mg/kg/day dose groups with macroscopic observations were examined microscopically for skin tumors.

Note: No animals in either of the interim sacrifice groups had any skin fibromas or papillomas. Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 5. Triclopyr - Fischer-344 Rat Study

Female Adrenal Gland Pheochromocytoma Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	3	12	36
Benign (%)	2/49 (4)	6[a]/50 (12)	2/50 (4)	6/50 (12)
p =	0.174	0.141	0.684	0.141
Malignant (%)	1/49 (2)	0/50 (0)	0/50 (0)	2[b]/50 (4)
p =	0.156	0.495[n]	0.495[n]	0.508
Combined (%)	3/49 (6)	6/50 (12)	2/50 (4)	8/50 (16)
p =	0.079	0.254	0.490	0.106

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

[a]First benign pheochromocytoma observed at week 95, 3 mg/kg/day.

[b]First malignant pheochromocytoma observed week 100, 36 mg/kg/day.

[n]Negative change from control.

Note: No animals in either of the interim sacrifice groups had any adrenal gland pheochromocytomas. Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 6. Triclopyr - Fischer-344 Rat Study

Female Mammary Gland Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	3	12	36
Adenomas (%)	0/49 (4)	0/16[#] (0)	0/19[#] (0)	1[a]/50 (2)
p =	0.373	1.000	1.000	0.505
Adenocarcinomas (%)	0/49 (0)	0/16[#] (0)	0/19[#] (0)	4[b]/50 (8)
p =	0.018*	1.000	1.000	0.061
Combined (%)	0/49 (0)	0/16[#] (0)	0/19[#] (0)	5/50 (10)
p =	0.006**	1.000	1.000	0.030*

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

[a]First adenoma observed at week 106, dose 36 mg/kg/day.

[b]First adenocarcinoma observed at week 92, dose 36 mg/kg/day.

[#]Only those animals in the 3 and 12 mg/kg/day dose groups with macroscopic observations were examined microscopically for mammary gland tumors.

Note: No animals in either of the interim sacrifice groups had any mammary gland tumors. Interim sacrifice animals are not included in this analysis.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 7. Triclopyr - Jcl:ICR Mouse Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks						
Dose (ppm)	1-26	26[i]	27-52	52[i]	53-78	79-96[f]	Total
0	2/100	10/98	15/88	10/73	23/63	15/40	55/80 (69)
50	3/100	10/97	11/87	10/76	23/66	17/43	54/80 (68)
250	0/100	10/100	22/90	10/68	26/58	10/32	58/80 (72)
1250	3/100	10/97	15/87	10/72	18/62	19/44	55/80 (69)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifices at weeks 26 and 52.

[f]Final sacrifice at week 96.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 8. Triclopyr - Jcl:ICR Mouse Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (ppm)	Weeks 1-26	26[i]	27-52	52[i]	53-78	79-96[f]	Total
0	5/100	10/95	15/85	10/70	18/60	11/42	49/80 (61)
50	2/100	10/98	15/88	10/73	26/63	11/37	54/80 (68)
250	2/100	10/98	17/88	10/71	23/61	11/38	53/80 (66)
1250	5/99[a]	10/94	17/84	10/67	19/57	11/38	52/79 (66)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifices at weeks 26 and 52.

[f]Final sacrifice at week 95.

[a]One accidental death at week 12, dose 1250 ppm.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 9. Triclopyr - Jcl:ICR Mouse Study

Female Mammary Gland Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	50	250	1250
Adenocarcinomas (%)	0/57 (0)	1/56 (2)	2/56 (4)	4[a]/53 (8)
p =	0.016*	0.496	0.243	0.051

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 32; also excludes both week 26 and week 52 interim sacrifice animals.

[a]First adenocarcinoma observed at week 32, dose 1250 ppm.

Note: There were no adenocarcinomas observed in any interim sacrifice animals.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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